

R E M A R K S

Claims 27, 28, 30 to 35, 37, 50 and 51 as set forth in Appendix I of this paper are herewith presented for further prosecution. Relative to the previous version and as indicated in the listing of claims, Claims 29, 36 and 38 to 49 have been canceled, Claims 27, 28, 30 to 35, and 37 have been amended, and Claims 51 and 52 have been added.

In addition to editorial changes in the claims, applicants have corrected Claims 27 and 28 on the basis, *e.g.*, of the disclosure on page 3, indicated lines 32 to 34, of the application. Moreover, applicants have further specified the monooxygenase in Claim 27 on the basis, *e.g.*, of the disclosure on page 3, indicated line 43, to page 4, line 2, of the application. Claim 31 was revised correspondingly. New Claims 50 and 51 have been added to further bring out some embodiments of the monooxygenase which are addressed, *e.g.*, in the disclosure on page 3, indicated line 41, to page 4, indicated line 15, of the application. No new matter has been added. Favorable consideration is respectfully solicited.

Claim 27 was objected to for failing to italicize the referenced bacillus. Claim 27 has been corrected accordingly, and it is respectfully requested that the objection to Claim 27 be withdrawn. Favorable action is solicited.

Previously pending claims 33 to 35 were rejected under 35 U.S.C. §112, ¶1, as allegedly being drawn to subject matter insufficiently supported by the written description provided in the application. For the following reasons, the rationale underlying the rejection is deemed to be in error and/or fails to be applicable where the subject matter of current Claims 33 to 35 is concerned.

The rejection asserts that the claims reasonably allow for monooxygenases isolated from any and all sources, and/or any and all variants thereof. Claims 33 to 35 as herewith presented are drawn to a particular process which *inter alia* requires a certain monooxygenase which is derived by mutating cytochrome P450 monooxygenase BM-3 from *Bacillus megaterium* having the amino acid sequence according to SEQ ID NO:2 and which has a particular functional mutation in specific positions of the amino acid sequence. The rationale upon which the rejection is based, thus, fails to be applicable. For at least the foregoing reason, it is respectfully requested that the rejection be withdrawn. Favorable action is solicited.

Previously pending claims 33 to 35 were rejected under 35 U.S.C. §112, ¶1, as allegedly being drawn to subject matter insufficiently enabled by the information provided in the application. For the following reasons, the rationale underlying the rejection is deemed to be in error and/or fails to be applicable where the subject matter of current Claims 33 to 35 is concerned.

The rejection asserts that the claims allow for a method in which a modified cytochrome P450 monooxygenase of unknown structure is employed. Current Claims 33 to 35 refer to a monooxygenase having a very specific structure in that the functional mutation consists of particular mutations in at least one of positions 74, 87, and 188. The rationale that the claims reasonably allow for monooxygenases of unknown structure, thus, fails to be applicable. For at least the foregoing reason, it is respectfully requested that the rejection be withdrawn. Favorable action is solicited.

Previously pending claims 27 to 37 were rejected under 35 U.S.C. §102(b) as being anticipated by the teaching of *Graham-Lorence et al.* (*J. Biol. Chem.* 272(2), 1127-1135 (1997)). In particular, the rejection argues that the particular oxidizing activity which is utilized in applicants' process is *inherently* present in a mutant cytochrome P450 monooxygenase described in the reference, and concludes that the mutant, thus, carries out the claimed process under "normal" operating conditions. For the following reasons, the rationale underlying the rejection is deemed to be in error and/or fails to be applicable where the subject matter of current Claims 27, 28, 30 to 35, 37, 50 and 51 is concerned.

The processes set forth in applicants' independent Claims 27 and 33 *inter alia* require that a substrate compound having an N-, O- or S-heterocyclic mono- or polynuclear aromatic moiety (Claim 27) or an indole substrate (Claim 33) be oxidized by

- a1) culturing a recombinant microorganism which expresses the particular monooxygenase in a culture medium, in the presence of an exogenous or intermediately formed substrate; or
- a2) incubating a substrate-containing reaction medium with the particular monooxygenase, whereby at least one aromatic C-H group of the heterocyclic aromatic moiety is oxidized (Claim 27), or indigo and/or indirubin is produced (Claim 33).

*Graham-Lorence et al.* describe that a mutant of cytochrome P450 BM-3 in which Phe87 is replaced by Val regio- and stereoselectively converts arachidonic acid into (14S, 15R)-epoxyeicosatrienoic acid and converts eicosapentaenoic acid into a mixture of (14S, 15R)- and (17S, 18R)-epoxyeicosatetraenoic acid, *see, e.g.*, para. 3 on page 1127 of the reference. Accordingly,

under “normal” operation conditions, the substrate which is converted by the mutant is a polyunsaturated fatty acid rather than a substrate compound having an N-, O- or S-heterocyclic mono- or polynuclear aromatic moiety as is referenced in applicants’ claims. These “normal” operation conditions are, e.g., illustrated by the “Enzyme Activity Determinations” which are described in para. 5 on page 1128 of the reference. As the reference illustrates, under normal operating conditions the mutant is not cultured in the presence of an exogeneous or intermediately formed substrate having an N-, O- or S-heterocyclic mono- or polynuclear aromatic moiety, nor is a reaction medium comprising such a substrate incubated with the mutant. Under normal operating conditions the mutant, therefore, cannot be deemed to *inherently* perform a process in which an aromatic C-H group of the heterocyclic aromatic moiety is oxidized or in which indigo or indirubin is produced.

There is no requirement that a person of ordinary skill in the art would have recognized an inherent disclosure at the time of invention. It is, however, required that the subject matter is, in fact, inherent in the prior art reference,<sup>2)</sup> i.e., the function, property or characteristic in question is necessarily present in the thing which is described in the reference. The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.<sup>3)</sup>

*In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art<sup>[4)]</sup>*

and

*[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'<sup>[5)]</sup>*

The reference itself corroborates that normal operating conditions fail to entail culturing the prior

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- 2) MPEP 2112, Rev. 6, Sept. 2007, page 2100–46, citing *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003).
  - 3) MPEP 2112, Rev. 6, Sept. 2007, page 2100–47, citing *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993).
  - 4) MPEP 2112, Rev. 6, Sept. 2007, page 2100–48, citing *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)
  - 5) MPEP 2112, Rev. 6, Sept. 2007, page 2100–47, citing *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (citations omitted); emphasis added.

art mutant in the presence of an exogeneous or intermediately formed substrate having an N-, O- or S-heterocyclic mono- or polynuclear aromatic moiety or incubating a reaction medium comprising the substrate with the mutant. Correspondingly, normal operating conditions as established by the reference cannot inherently entail oxidizing at least one aromatic C-H group of the N-, O- or S-heterocyclic mono- or polynuclear aromatic moiety or producing indigo or indirubin. The missing descriptive matter, *e.g.*, the particular nature of the substrate compound and the particular result which is achieved in accordance with applicants' process, thus, is not necessarily present or *inherent* in the referenced art.

The rejection seeks to support the conclusion that *Graham-Lorence et al.* inherently describe applicants' process referring to the Court's holding in *In re King*, 801 F.2d 1324 (Fed. Cir. 1986). However, in that case the only arguable difference between the article described in the prior art and the method which was claimed was the prior art's "*failure to articulate a scientific explanation of why the structure behaves as it does, namely, that optical interferences causes color which changes when the thickness of the metal oxide layer is varied.*" *In re King*, 801 F.2d at 1328. The prior art taught a semi-reflective layered article, *i.e.* window panes, and described that the ratio of the light transmitted to that reflected, as well as the transmitted and reflected colors, can be altered by varying the thickness of article's films and/or the selection of the article's metal oxide overcoat, *ibid.* at 1326. The claimed method aimed at enhancing color effects produced by ambient light and controlling the light intensity using the prior art article, *ibid.* at 1325. The Court affirmed that the semi-reflective layered article of the prior art when exposed to ambient light, *i.e.*, the normal use of the prior art article, necessarily transmitted and reflected the light and reflected certain colors, *i.e.*, performed the claimed method. The factual situation in *In re King* is clearly distinguished from the circumstances in the present case in that the normal use as is established by *Graham-Lorence et al.* does not entail culturing the prior art mutant in the presence of an exogeneous or intermediately formed substrate having an N-, O- or S-heterocyclic mono- or polynuclear aromatic moiety or incubating a reaction medium comprising such a substrate with the mutant. The normal use as is established by *Graham-Lorence et al.*, thus, cannot inherently entail oxidizing at least one aromatic C-H group of the N-, O- or S-heterocyclic mono- or polynuclear aromatic moiety, or producing indigo or indirubin. "[I]f the operation performed by the machine is new in reference to the object upon which it is employed, a new process has been invented; and this is no less true if the machine or instrument employed is new than if it were old," see *In re Tarczy-Hornoch*, 397 F.2d 856, 867 (CCPA 1968).

For at least the foregoing reasons, it is respectfully requested that the rejection be withdrawn.  
Favorable action is solicited.